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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/214,009	05/07/1999	NICO JOHANNES C M BEEKMAN	3898US	6111

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EXAMINER
DEVI, SARVAMANGALA J N

ART UNIT	PAPER NUMBER
1645	29

DATE MAILED: 05/01/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/214,009	Beekman et al.
Examiner	**Art Unit**
S. Devi, Ph.D.	1645

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *three* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Feb 7, 2003* .

2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1, 3-6, 9, 10, and 12* is/~~are~~ pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1, 3-6, 9, 10, and 12* is/~~are~~ rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☒ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☒ All b) ☐ Some* c) ☐ None of:

1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 02/07/03 (paper no. 28) has been entered.

Applicants' Amendment

2) Acknowledgment is made of Applicants' amendment filed 11/12/02 (paper no. 24) in response to the final Office Action mailed 06/10/02 (paper no. 22).

Status of Claims

3) Claims 2, 13-15 and 19-23 have been canceled via the amendment filed 11/12/02.

Claim 1 has been amended via the amendment filed 11/12/02.

Claims 1, 3-6, 9, 10 and 12 are pending and are under examination.

Prior Citation of Title 35 Sections

4) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

5) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Rejection(s) Moot

6) The rejection of claims 19 and 20 made in paragraph 15 of the Office Action mailed 10/23/01 (paper no. 17) and maintained in paragraph 13 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 103(a) as being unpatentable over Haynes *et al.* (US 5,013,548) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), is moot in light of Applicants' cancellation of the claims.

7) The rejection of claims 2 and 19-23 made in paragraph 16 of the Office Action mailed 10/23/01 (paper no. 17) and maintained in paragraph 14 of the Office Action mailed 06/10/02 (paper

no. 22) under 35 U.S.C § 103(a) as being unpatentable over Meloen *et al.* (US 6,284,733) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), is moot in light of Applicants' cancellation of the claims.

8) The rejection of claim 13 made in paragraph 15 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 102(e) as being anticipated by Golding (US 5,824,310), is moot in light of Applicants' cancellation of the claim.

9) The rejection of claims 2, 19, 20, 22 and 23 made in paragraph 16 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 102(b) as being anticipated by Jung *et al.* (EP 0,431,327 - original and the translated document), is moot in light of Applicants' cancellation of the claims.

10) The rejection of claims 2, 19, 20 and 22 made in paragraph 17 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 102(b) as being anticipated by Chang *et al.* (US 5,149,782), is moot in light of Applicants' cancellation of the claims.

11) The rejection of claims 19, 20, 22 and 23 made in paragraph 18 of the Office Action mailed 06/10/02 (paper no. 22) 35 U.S.C § 102(b) as being anticipated by Shen *et al.* (US 5,907,030, filed 1995), is moot in light of Applicants' cancellation of the claims.

12) The rejection of claims 13, 14, 19, 20 and 23 made in paragraph 21 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 103(a) as being unpatentable over Shen *et al.* (US 5,907,030, filed 1995) or Chang *et al.* (US 5,149,782) in view of Wong (*In*: *Chemistry of Protein Conjugation and Cross-linking*. CRC Press, Inc., London, Chapter 3, 49-73, 1993) and/or Staufenbiel (*J. Biol. Chem.* 263: 13615-13622, 1988), is moot in light of Applicants' cancellation of the claims.

13) The rejection of claims 15 and 21 made in paragraph 22 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782) in view of Wong (*In*: *Chemistry of Protein Conjugation and Cross-linking*. CRC Press, Inc., London, Chapter 3, 49-73, 1993) and/or Staufenbiel (*J. Biol. Chem.* 263: 13615-13622, 1988) as applied to 19, and further in view of Meleon *et al.* (US 6,284,733), is moot in light of Applicants' cancellation of the claim.

14) The rejection of claims 19 and 21 made in paragraph 23 of the Office Action mailed 06/10/02

(paper no. 22) under 35 U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782) in view of Russell-Jones *et al.* (WO 91/02799) or Meloen *et al.* (US 6,284,733, already of record) (Meloen *et al.*, '733), is moot in light of Applicants' cancellation of the claims.

Rejection(s) Withdrawn

15) The rejection of claims 1 and 5 made in paragraph 15 of the Office Action mailed 10/23/01 (paper no. 17) and maintained in paragraph 13 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 103(a) as being unpatentable over Haynes *et al.* (US 5,013,548) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), is withdrawn in light of Applicants' amendment to the base claim.

16) The rejection of claims 1, 3-6, 9, 10 and 12 made in paragraph 16 of the Office Action mailed 10/23/01 (paper no. 17) and maintained in paragraph 14 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 103(a) as being unpatentable over Meloen *et al.* (US 6,284,733) in view of Wiedemann *et al.* (*J. Pathol.* 164: 265-271, 1991), is withdrawn in light of Applicants' amendment to the base claim.

17) The rejection of claims 1, 3, 5 and 12 made in paragraph 15 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 102(e) as being anticipated by Golding (US 5,824,310), is withdrawn in light of Applicants' amendment to the base claim.

18) The rejection of claims 1, 3-5 and 12 made in paragraph 16 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 102(b) as being anticipated by Jung *et al.* (EP 0,431,327 - original and the translated document), is withdrawn in light of Applicants' amendment to the base claim.

19) The rejection of claims 1, 3-5, 9 and 10 made in paragraph 17 of the Office Action mailed 06/10/02 (paper no. 22) under 35 U.S.C § 102(b) as being anticipated by Chang *et al.* (US 5,149,782), is withdrawn in light of Applicants' amendment to the base claim.

20) The rejection of claims 1 and 12 made in paragraph 18 of the Office Action mailed 06/10/02 (paper no. 22) 35 U.S.C § 102(b) as being anticipated by Shen *et al.* (US 5,907,030, filed 1995), is withdrawn in light of Applicants' amendment to the base claim.

21) The rejection of claims 1, 3, 5 and 12 made in paragraph 19 of the Office Action mailed 06/10/02 (paper no. 22) 35 U.S.C § 102(b) as being anticipated by Staufenbiel (*J. Biol. Chem.* 263:

13615-13622, 1988), is withdrawn in light of Applicants' amendment to the base claim.

22) The rejection of claims 1, 3 and 5 made in paragraph 20 of the Office Action mailed 06/10/02 (paper no. 22) 35 U.S.C § 102(b) as being anticipated by Wan *et al.* (*J. Cellular Physiol.* 145: 9-15, 1990), is withdrawn in light of Applicants' amendment to the base claim.

23) The rejection of claims 1, 3, 4, 6, 9 and 10 made in paragraph 23 of the Office Action mailed 06/10/02 (paper no. 22) 35 U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782) in view of Russell-Jones *et al.* (WO 91/02799) or Meloen *et al.* (US 6,284,733, already of record) (Meloen *et al.*, '733), is withdrawn in light of Applicants' amendment to the base claim.

Rejection(s) under 35 U.S.C § 112, Second Paragraph

24) Claims 1, 3-6 and 9-12 are rejected under 35 U.S.C § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicants regard as the invention.

(a) Claim 1 is vague and indefinite in the recitation "after administration to a subject", because it is unclear what is being administered to the subject: antigen, peptide carrier, or said vaccine?

(b) Claim 1 is vague in the recitation 'physiological conditions'. Since physiological conditions can vary from one system or one subject to another, it is unclear what conditions qualify as physiological conditions. Do these include or exclude acidic, basic or neutral conditions?

(c) Claim 3 is vague and indefinite in the recitations: "protein" and "polypeptide", because it is unclear what the differences are between the two.

(d) Claims 4-6, 9, 10 and 12, which depend directly or indirectly from claim 1, are also rejected as being indefinite because of the vagueness or indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C § 102

25) Claims 1, 3, 4 and 12 are rejected under 35 U.S.C § 102(e) as being anticipated by Yatvin *et al.* (US 6,339,060).

Yatvin *et al.* disclosed a composition comprising a conjugate of a biologically active compound linked to a polar lipid in a cleavable manner for delivery to phagocytic cells wherein the biologically active compound is specifically or non-specifically cleaved in a phagocytic mammalian

cell *in vivo* under physiological conditions (see abstract; claims; and first two paragraphs under 'Summary of the Invention' in columns 7 and 8). A pharmaceutically composition comprising the conjugate in a pharmaceutically acceptable carrier is taught which is administered to a human (see claims 49, 69 and 71). The biologically active compound is an antigenically active peptide; a toxin, such as, diphtheria toxin, or a peptide, such as, a defensin peptide (see claims; first paragraph in column 11; and Example 2). The toxin is man-made, i.e., synthetic (see first paragraph in column 19). The weak linker functionality which is cleaved inside phagocytic cells under specific conditions is thioester (see paragraph bridging columns 22 and 23). The lipid is phosphatidyl choline, phosphatidyl serine, phosphatidyl glycerol etc. (see claims). The linker functional group covalently links the biologically active compound to a polar lipid and is designed to facilitate, control, modulate and regulate the release of the biologically-active compound at a desired intracellular target site (see last two full paragraphs in column 22).

Claims 1, 3, 4 and 12 are anticipated by Yatvin *et al.*

Rejection(s) under 35 U.S.C § 103

26) Claims 1, 3-5, 9, 10 and 12 are rejected under 35 U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782, already of record) in view of Yatvin *et al.* (US 6,339,060).

The reference of Yatvin *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C § 102 and accordingly is not disqualified under U.S.C 103(a).

Chang *et al.* disclosed therapeutic conjugates comprising an antigen, such as, a protein, polypeptide, synthetic peptides, glycoprotein or nucleic acid, coupled to a palmitic acid or other fatty acids of varying length via a linkage that is cleavable (i.e., labile) under appropriate conditions, for example, conditions extant at the target site (i.e., physiological conditions). The cleavable linkage is a disulfide linkage. See claims, claims 1, 2, 7, 10 and 11 in particular; column 2, lines 2-49; column 3, lines 9-13 and 17 and 18; column 3, lines 56 and 57; column 5, lines 9-23; and column 6, lines 31-45. Peptides that are synthetic are used (see column 3, lines 56 and 57). The linkage can be of irreversible or cleavable (i.e., reversible) types (see column 8, lines 2 and 3). A cleavable linkage is a disulfide bond, which may be found between the SH group of Cys residues in a protein molecule. Active electrophilic S atoms can also be introduced by the use of SPDP. At the target tissue sites, the S-S bonds are cleaved. Cleavable bonds can also be constructed taking advantage of the slight

acidic pH in target tissues (see third full paragraph in column 6). Two or more membrane blending agents (i.e., for example, peptide-peptide-fatty acid) can be interlinked in the conjugate (see column 2, lines 48 and 49). The membrane blending agent is coupled to a blocking agent via a cleavable linkage so that the blocking agent gets released (see column 2, lines 7-12 and 45-47). The blocking agent can be a monoclonal antibody, a ligand for a cell surface receptor or a short peptide (see column 2, lines 27-35 and 39-40). The blocking agent can also be a targeting agent such as, a **hormone** or growth factor which selectively directs the molecular conjugate to an appropriate target, (see column 6, lines first full paragraph). The composition is used *in vivo* (i.e., administered to a subject) for therapeutic and diagnostic purposes (see column 7, second full paragraph). That the therapeutic conjugate is administered (see column 6, lines 41-45) indicates that it was contained in a pharmaceutically acceptable carrier.

Chang *et al.* differ from the instant invention in not using a thioester bond as the labile bond.

However, the use of a thioester bond or linkage as an alternative labile or cleavable linkage in a conjugate meant for *in vivo* administration was known in the art. For instance, see the teachings of Yatvin *et al.* above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Chang's disulfide linkage with Yatvin's alternate, labile or cleavable thioester linkage, to produce the composition of the instant invention, with a reasonable expectation of success. Given that thioester bonds were already used in the art successfully in the production of cleavable antigen-lipid conjugates as taught by Yatvin *et al.*, the substitution of one labile bond, such as, disulfide bond, with another, alternate, art-known labile bond, such as, thioester bond would have been obvious to one of ordinary skill in the art, would have been well within the realm of routine experimentation and would have expected to bring about similar effects or results, absent evidence to the contrary.

Claims 1, 3-5, 9 and 10 are *prima facie* obvious over the prior art of record.

27) Claims 1, 3-5 and 12 are rejected under 35 U.S.C § 103(a) as being unpatentable over Shen *et al.* (US 5,907,030, filed 1995, already of record) in view of Yatvin *et al.* (US 6,339,060).

The reference of Yatvin *et al.* is applied in this rejection because it qualifies as prior art under subsection (e) of 35 U.S.C § 102 and accordingly is not disqualified under U.S.C 103(a)..

Shen *et al.* disclosed sulfhydryl-containing peptides or proteins comprising fatty acid-conjugated products with a disulfide linkage for delivery of the compounds to mammalian cells. The disulfide linkage in the conjugate is quite **labile** in the cells and thus facilitates intracellular release of the intact compounds from the fatty acid moieties (see abstract; and paragraph bridging columns 4 and 5). It is taught that fatty acids represent potentially the most useful carriers for the delivery of proteins and peptides (see column 4, lines 11-16). Sulfhydryl-containing compounds are peptides, proteins or oligonucleotides (see column 4, lines 59-65; and claims). The sulfhydryl-containing biopolymer is attached to a fatty acid derivative via a **reversible** biodegradable disulfide bond so that the compound gets released into interstitial fluid as the result of disulfide bond reduction (see column 5, lines 31-38). The conjugate is administered to a mammal in an aqueous solution (see column 5, lines 61-63). The biopolymeric proteins and peptides are synthesized by solid-state synthesis (see column 7, lines 34-40). The conjugates are contained in pharmaceutically acceptable carrier or adjuvants (see first full paragraph in column 9). It is a particular advantage that the disulfide linkage between the fatty acid moiety and the peptide or protein may readily be reduced. The active peptide or protein molecules are released in intact form inside the target tissues or cells (see column 9, lines 44-48). Shen *et al.* disclose a method of producing a palmityl disulfide conjugate of BBI protein (see columns 11 and 13). The reduction of BBIssPal conjugate with DTT causes the detachment of the palmitic acid from the conjugate (see column 13, lines 49 and 50). BBIssPal was administered to mice (see Example 4). A palmitic acid conjugate of HRP, HRPssPal, is also taught in Example 9.

Shen *et al.* differ from the instant invention in not using a thioester bond as the labile bond.

However, the use of a thioester bond or linkage as an alternative labile or cleavable linkage in a conjugate meant for *in vivo* administration was known in the art. For instance, see the teachings of Yatvin *et al.* above.

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Shen's disulfide linkage with Yatvin's alternate, labile or cleavable thioester linkage, to produce the composition of the instant invention, with a reasonable expectation of success. Given that thioester bonds were already used in the art successfully in the production of cleavable antigen-lipid conjugates as taught by Yatvin *et al.*, the substitution of one labile bond, such as, disulfide bond, with another, alternate, art-known labile bond, such as, thioester bond would have

been obvious to one of ordinary skill in the art, would have been well within the realm of routine experimentation and would have expected to bring about similar effects or results, absent evidence to the contrary.

Claims 1, 3-5 and 12 are *prima facie* obvious over the prior art of record.

28) Claim 6 is rejected under 35 U.S.C § 103(a) as being unpatentable over Chang *et al.* (US 5,149,782, already of record) or Shen *et al.* (US 5,907,030, filed 1995, already of record) as modified by Yatvin *et al.* (US 6,339,060) as applied above to claims 1, 3 and 4 and further in view of Russell-Jones *et al.* (WO 91/02799, already of record) or Meloen *et al.* (US 6,284,733, already of record) (Meloen *et al.*, '733).

The disclosure of Chang *et al.* or Shen *et al.* as modified by Yatvin *et al.* is described above, which does not teach the peptide to be a peptide of the amino acid sequence of SEQ ID NO: 1.

However, Russell-Jones *et al.* disclosed the concept and method of fusing or conjugating at least one or tandem repeats of LHRH (i.e., GnRH), Glu-His-Trp-Ser-Tyr-Gly-Leu-Arg-Pro-Gly (i.e., SEQ ID NO: 1) to a lipid-containing carrier (see page 2; paragraph bridging pages 3 and 4; page 7; page 13; and page 29). Russell-Jones *et al.* taught the use of LHRH dimers (see Figure 4 and page 13) or multimers (see Figure 5; Table 1; pages 13 and 21; Examples 1 and 6; and claims 5-9 and 12-14). Russell-Jones *et al.* taught the advantage of using tandem repeats of LHRH (i.e., peptide sequences) over a single insert (see page 6, lines 26-29).

Meloen *et al.* ('733) also taught the use of dimeric LHRH or GnRH peptide of the amino acid sequence, SEQ ID NO: 1, and its conjugation via a labile bond (see abstract; columns 6 and 9; and claims).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Chang's or Shen's peptide with Russel-Jones' GnRH tandem repeat, or Meloen's dimeric GnRH peptide to produce the composition of the instant invention, with a reasonable expectation of success, because Chang *et al.* taught that the conjugate can contain a hormone and that two or more agents can be interlinked in the conjugate. A skilled artisan would have readily understood that Russel-Jones' or Meloen's GnRH qualifies as a hormone. Substitution of a generic peptide with a specific, art-known hormone peptide in a conjugate containing labile thioester bonds is well within the realm of routine experimentation and would yield a similarly

effective product.

Claim 6 is *prima facie* obvious over the prior art of record.

Relevant Prior Art

29) The prior art made of record and not relied upon in any of the rejections is considered pertinent to Applicant's disclosure:

- Theodore *et al.* (US 6,416,738) disclosed a therapeutic, targeting conjugate wherein an active agent is conjugated to a ligand via a conditionally cleavable linker, thioester. Theodore *et al.* taught that the use of the conjugate results in the selective release of the active agent at tumor cell target sites, because thioesters are hydrolytically cleaved under acidic or basic conditions (i.e., physiologic conditions), or by esterase enzymes (see column 24; paragraph bridging column 24 and 25; section G in column 25; and 'Summary of the Invention'). The conjugate contains an antibody directly linked to an active agent, such as, a drug, anti-tumor agent, toxin or the like (see columns 4 and 5). The conjugate is administered *in vivo* (see columns 9 and 10). Preferred targeting moiety is a hormone, an antibody, a polypeptide, a peptide or a synthetic peptide (see paragraph bridging columns 10 and 1; and fifth full paragraph in column 53).

- Reilly *et al.* (US 5,955,080) disclosed a self-adjuvanting vaccine for chemical castration application comprising an LHRH peptide conjugated to a fatty acid (see abstract; last full paragraph in column 2).

- Pavanasasivam (US 4,744,981) disclosed conjugates of a fungal mycotoxin, trichothecene and an antibody that recognizes an antigen present on tumor cells wherein trichothecene is covalently linked to the antibody by thioester bonds for inhibiting the growth and metabolism antigen positive cells (see abstract; claims 16, 20 and 1; and column 2). Pavanasasivam expressly disclosed that a thioester bond represents a labile bond (see lines 25-28 in column 8).

- Sivam (US 4,906,452) provided a disclosure similar to that of Pavanasasivam.

- Benson *et al.* (WO 91/00871) disclosed a composition comprising a palmityl thioesters of lung surfactant protein wherein the protein is covalently attached to palmitic acid. A palmitoylated recombinant surfactant protein (see entire document).

Remarks

30) Claims 1, 3-6, 9, 10 and 12 stand rejected.

31) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center located in Crystal Mall 1. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The CM1 facsimile center's telephone number is (703) 308-4242, which is able to receive transmissions 24 hours a day and 7 days a week. The RightFax number for submission of before-final amendments is (703) 872-9306. The RightFax number for submission of after-final amendments is (703) 872-9307.

32) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (703) 308-9347. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (703) 308-3909.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (703) 308-0196.

April, 2003

SD

S. DEVI, PH.D.
PRIMARY EXAMINER